CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

73045

CORRESPONDENCE

ANDA 73-045

MAY 12 1997

A.L.Laboratories, Inc.
Attention: Deborah Winkel
The Johns Hopkins Research Campus
333 Casselll Drive, Suite 3500
Baltimore, MD 21224

Dear Madam:

Reference is made to your Abbreviated New Drug Application, and the amendments submitted on September 9, 11 and 20, October 8 and November 15, 1996 and January 6 and 22, 1997 for Albuterol Inhalation Aerosol (MDI), 90 ug/actuation.

Reference is also made to the telephone conference of February 28, 1997 between Ron Bynum, and Wallace Adams, Gur Jai Pal Singh and Lizzie Sanchez of the Office of Generic Drugs; and to the FAX request for information issued on March 5, 1997 as a follow-up to that telephone conference. The Division has not received any new data in response to our request.

The Office of Generic Drugs has reviewed the bioequivalence data previously submitted and the same comments provided in the above communications are forwarded:

1. Because drug delivery may change progressively through canister life, the Division of Bioequivalence believes that, as a bioequivalence criterion, a test product should meet USP <905> Content Uniformity requirements at beginning, middle and end of canister through-life. Therefore, please provide the following:

   a. Content uniformity data on 30 canisters of test lot # 8457 at beginning, middle and end.

   b. Content uniformity data on 10 canisters of test lots # 8671 and 8834 at beginning, middle and end. For each batch, if 10 canisters fail to meet the USP specification at each of beginning, middle and end, an additional 20 canisters should be tested as stated in USP <905>. Note that, consistent with the 27 June 1989 Division of Bioequivalence *Guidance for the In Vitro Portion of Bioequivalence Requirements for Metaproterenol Sulfate and Albuterol Inhalation Aerosols (Metered Dose Inhalers)*, the specifications will be evaluated separately at beginning, middle and end of canister through life.

   c. Data may be provided in the same format as that on pages 430 and 431 of the 6 January 1997 submission.

2. Additional information is also requested by the Division of Bioequivalence:

   a. The specific model of Andersen 8 stage cascade impactor used by the firm for the data submitted on 6 January 1997.

   b. The expiration dates for test product batches # 8671 and 8834.

   c. Testing dates for the twin impinger data submitted on 12 June 1995 and 27 July 1996.

   d. Conduct of the Microscopy Test (USP <601>) on canisters from test product batches # 8457, 8671, and 8834, and Ventolin MDI batch # 6ZP0756. The Division requests these comparative baseline data, noting that the test serves a number of purposes: determination of the number of particles larger than microns; identification of unusual agglomeration; characterization of crystal morphology; and identification of foreign particulates not related to the drug substance.

As described under 21 CFR 314.96 an action which will amend this application is required. The amendment will be required to address all of the comments presented in this letter. Should you have any questions, please call Lizzie Sanchez, Pharm.D., Project Manager, at (301) 827-5847. In future correspondence regarding this issue, please include a copy of this letter.

Sincerely yours,

/S/

for Nicholas Fleischer, Ph.D.
Director
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDA 73-045

JAN 13 1989

APPLICANT:
Generics (UK) Limited
Station Close
Potters Bar Heris
Herts EN6 1TL
England

US AGENT:
Superpharm Corporation
Attention: Ms. Diana Sloane
1769 Fifth Avenue
Bayshore, NY 11706

Dear Madam:

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for the following:

NAME OF DRUG: Albuterol Aerosol Metered Inhalation, 0.09 mg/INH

DATE OF APPLICATION: December 23, 1988

DATE OF RECEIPT: December 23, 1988

We will correspond with you further after we have had the opportunity to review the application.

Please identify any communications concerning this application with the ANDA number shown above.

Sincerely yours,

/S/ FOR 1-13-89

Marvin Seife, M.D.
Director
Division of Generic Drugs
Office of Drug Standards
Center for Drug Evaluation and Research

/S/ 1/13/89

/S/ 1/12/89

cc:
DUP HFN-230
Rosen/Meyer
kl/1-12-89
Ack 2046b

ANDA 73-045

SEP 19 1989

Generics (UK) Limited
Station Close, Potters Bar
Herts EN6 ITL, England

c/o U.S. Agent
Superpharm Corporation
Attention: Ms. Diana Sloane
1769 Fifth Avenue
Bayshore, NY 11706

Dear Madam:

Reference is made to the in vitro test data submitted on December 23, 1988 for Albuterol Aerosol Inhaler, 0.09 mg/INH.

The data has been reviewed by the Division of Bioequivalence and they have the following comments:

"1. The firm is requested to provide batch records for test product lots 291E1 and 293E1. The firm should provide documentation that the lots of the two reference products (Allen & Hanburys lot Z12927NA and Schering lot 7BBS460) were purchased in the United States and intended for U.S. distribution.

2. The automatic image analysis experimental procedure is not fully described. The procedure on p. 47, Vol. 1.3, states that sprays per sample are used; p. 516, Vol. 1.2 states that sprays per sample are used. This inconsistency should be explained. The number of slides examined per experiment should be stated. Whether data from all fields of view on the slides were examined with the system should be stated. Page 48, Vol. 1.3, reports This term should be defined and its equation submitted. How this term differs from Std. Dev. should be described.

3. The cascade impactor data are incomplete since data for the reference products are missing. In addition, the following questions should be addressed.

   a. p. 72, Vol. 1.3 states that a 4 liter "perspex" chamber and human mouthpiece were used and that the flow rate was liter per min. Pages 516-517, Vol. 1.2 state that a liter chamber and flow rate of liters per min were used. No mention is made of a human mouthpiece. These discrepancies should be corrected and a drawing or photograph of the entire apparatus with dimensions should be submitted.

b. the entire contents of two canisters of the test product were discharged into the cascade impactor, resulting in an average collection (5 experiments) of under % of total mass (excluding propellants). In all experiments, mass balance should be obtained, quantifying drug on actuator, on sampling chamber, on sampling plates and walls and on filter. Mass balance requires a chemical assay. In addition to possible analytical balance sensitivity problems when measuring as little as mcg of drug plus surfactant, during the prolonged period of time necessary to discharge 400 + shots there is the possibility of drawing airborne contaminants into the cascade impactor, which would alter results.

c. the very low (under %) recovery may be related to the very low flow rate liter/min). The firm is requested to provide information regarding the use of the cascade impactor at this low flow rate and to describe its calibration procedure of % cutoff diameters using beads or other medium. A cascade impactor of not less than six stages with a particle size range of about microns should be used.

d. the enclosed Division of Bioequivalence In Vitro Guidance for Albuterol Inhalation Aerosols should be consulted for additional details.

4. Light scattering laser testing data should be submitted using three canisters of test and reference products. Testing should be conducted at the beginning, middle and end of each products labeled number of actuations. Additional details are provided in the Division of Bioequivalence In Vitro Guidance. Raw data outputs from the Malvern laser should be submitted for all experiments. Complete experimental details should be provided.

5. The data submitted from provide plume geometry information only. data must be provided with complete identification by lot number.

6. From a bioequivalence point of view, potency data on the test product lots 291E1 and 293E1 and the reference product lots are acceptable at this time.

7. The particle size and [ ] data should be provided for the test product lot 291E1 and reference products lots Z12927NA and 7BBS460 that were used in the in vivo bioequivalence study. Data on test product lot 293E1 may also be provided if desired by the firm.

RECOMMENDATION:

The in vitro test data submitted by Generics (UK), [Superpharm Corporation, U.S. Agent] on its Albuterol 90 mcg/Inhalation, not less than (NLT) 200 sprays per Inhaler, lot # 291E1, comparing it to Allen & Hanburys (Division of Glaxo) Ventolin^{R} 90 mcg/Inhalation, NLT 200 sprays per Inhaler, lot # Z12927NA and to Schering Proventil^{R} 90 mcg/Inhalation, NLT 200 sprays per Inhaler, lot # 7BBS460, have been found incomplete by the Division of bioequivalence. The firm should submit the information requested in comments listed above."

Sincerely yours,

/S/ /for 9-19-89

Acting Director
Division of Generic Drugs
Center for Drug Evaluation and Research

cc:
HFD-232
DRosen/FFang
kl/7-20-89/2526t
bio letter for
73-045

/S/ 7/24/89

SEP 25 199

ANDA 73-045

Generics (UK) Limited
c/o Superpharm Corporation
Attention: Ms. Diane Sloane
1769 Fifth Avenue
Bayshore, New York 11706

Dear Madam:

Reference is made to your abbreviated new drug application submitted pursuant to section 505(j) of the Federal Food, Drug and Cosmetic Act for Albuterol Inhalation Aerosol, 0.09 mg/Actuation.

Be advised that the innovator, Glaxo, Inc., has recently revised their Ventolin labeling (revision date January 1989, approval date April 14, 1989).

Please revise your labeling to reflect these changes and submit draft labeling for our review and comment. Also be aware that these changes may affect your carton labeling and container labels.

Sincerely yours,

/S/ /for 9-25-90

Acting Director
Division of Generic Drugs
Center for Drug Evaluation and Research

cc:
HFD-638
JMolzon/YMille 9.19.90
alh/9-18-90/7345.LJM
LETTER OUT

ANDA 73-045

A.L. Laboratories, Inc.
Attention: Deborah Miran
The Johns Hopkins Bayview Research Campus
333 Cassell Drive, Suite 3500
Baltimore, MD 21224

DEC 30 1997

Dear Madam:

This is in reference to your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Albuterol Inhalation Aerosol, 90 mcg/Inhalation.

Due to changes in the labeling of the listed drug Ventolin® Inhalation Aerosol (Glaxo Wellcome Inc.; Approved November 12, 1997; Revised September 1997), we request that you revise your insert to be in accord with the enclosed copy of the innovator's labeling.

Prepare and submit final printed package insert labeling as a supplement to this approved application.

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with the enclosed copy of the innovator's labeling with all differences annotated and explained.

Sincerely yours,

/S/ 12-29-97

Jerry Phillips
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDA 73-045

MAY 29 1992

A.L. Laboratories, Inc.
Attention: Deborah Winkel
One Executive Drive
P.O. Box 1399
Fort Lee, NJ 07024

Dear Madam:

We acknowledge receipt of your communication dated May 7, 1992, submitted as required by the provisions of Regulation 21 CFR 314.72(e) and Section 505(k) of the Federal Food, Drug and Cosmetic Act for Albuterol Inhalation Aerosol, 90 mcg/Inhalation.

Your letter details the transfer of ownership of the ANDA, from Generics (U.K.) Limited to A.L. Laboratories, Inc.

Pursuant to 21 CFR 314.72(b), the new owner shall advise FDA about any change in the conditions of the approved application.

The material submitted is being retained as part of your application.

Sincerely yours,

/S/

5-29-92

Roger L. Williams, M.D.
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA #73-045
DUP/Division File
HFD-600/Reading File
HFC-130/JAllen
HFD-84/Orange Book
HFD-634/MSmela/SSherken/5-15-92
HFD-632/RPollock/5-15-92
R/D initialed by GJohnston
bcw/5-15-92/73045trans.own
F/T by jkg/5-19-92
transfer of ownership

GJohnston 5/19/92

ANDA 73-045

JUL 18 1996

A. L. Laboratories, Inc.
Attention: Deborah Miran
The John Hopkins Bayview Research Campus
333 Cassell Drive,
Suite 3500
Baltimore MD 21224

Dear Madam:

Reference is made to the Abbreviated New Drug Application amendments submitted on June 12 and 22, 1995, for Albuterol Inhalation Aerosol, 90 mcg/Inhalation.

The Office of Generic Drugs has reviewed the bioequivalence data submitted and the following comments are provided for your consideration:

1. The June 12, 1995 *in vitro* data submission, Vol A8.2, provides particle size data by cascade impactor; pages 565 and 567 lists amounts of drug deposited on various stages of the impactor. Complete mass data on laboratory worksheets for each of the 18 studies for test and reference products, including amount of drug on the valve, actuator, and atomizing chamber should be provided, and also each date study was performed. Please provide legible representative plots of these studies showing the computation of MMAD and GSD.

2. The Andersen cascade impactor is calibrated at[L/minute. The firm used a flow-rate of[L/minute. USP 23 <601> specifies that the flow-rate through the cascade impactor should be within % of that specified by the manufacturer. Please comment. Please state the model number of the cascade impactor.

3. Cascade impactor validation tests in Volume 7.1, "Drug Product Specifications and Tests" are dated November 1994. Do these validation data apply to the comparative data summarized in Volume A8.2, pp. 565, 567?

4. Please provide respirable dose and respirable fraction data based on drug less than[ ]microns for each cascade impactor study. These data should be computed as described in USP 23, <601>.

5. Percentage material balance as defined in USP 23 <601> should be provided for each cascade impactor study. The mass of formulation delivered and the concentration of drug in the formulation should also be provided, along with the quantities in each individual canister used to compute these average mass and concentration values.

6. Regarding the batch record, please indicate the actual and theoretical batch size, including the number of filled canisters manufactured.

7. Please provide an explanation of the randomization process used to select test próduct canisters for the comparative *in vitro* bioequivalence testing, as well as for the *in vivo* bioequivalence study.

8. The formulation provided in volume 1.1, Section 5, p. 93, indicates an overage of(% %). Please clarify whether the overage applies to drug only or to all ingredients. If to all ingredients, does the product include an additional overage of drug only?

9. The Potency section of Volume A8.2 provides comparative data for only three canisters of test and reference products, instead of the ten canisters recommended by the 1989 *In Vitro* Guidance. In addition to estimation of mean drug delivery at beginning, middle and end of canister life, these ten canister data are also used to assure conformity to uniformity of unit spray content specifications (USP <905>). No conclusions can be drawn from the data of three canisters. The firm is requested to provide comparative unit spray content for ten canisters of the test and ten canisters of the reference products used in the *in vivo* bioequivalence study, determined within the expiration date of the products. The lot number of the reference listed drug does not correspond to that of the bioequivalence lot number. The firm is requested to confirm that these data were based on

10. Comparative spray pattern profiles are inadequate. Accurate measurements cannot be assured based on the photocopies provided in Volume A8.2, pp. 619-620. In the experience of the Division of Bioequivalence, spray patterns from an inhalation aerosol do not exhibit the irregular patterns shown on pp. 619-20. Please provide photographs of the UV spots for review, along with a complete listing of the experimental procedure, including the number of actuations fired to waste between each experiment.

11. Regarding the particle size distribution data by Malvern Laser, please provide information regarding the methodology (Volume A8.2, pp. 568-605) using the vertical down-pipe. If this method for sizing aerosols is a standardized, validated method, please provide references and other relevant information. Please comment on the effect of spraying every

two or five seconds, which is more frequent than the labeled interval between successive doses, on the resultant particle size distribution. Please comment on the effect of spraying with the canister held in a near-horizontal position rather than the labeled near-vertical position.

12. Regarding the twin stage impinger study (Volume A8.2, pp. 606-615), please provide the amount of drug in both the upper and lower stages for each canister, and the average shot dose as determined by [redacted] In addition, please provide respirable fraction for each canister for the data tabulated on p. 615, as defined in USP 23, <601), Single-stage Impactor Apparatus 2.

As described under 21 CFR 314.96 an action which will amend this application is required. The amendment will be required to address all of the comments presented in this letter. Should you have any questions, please call Mark Anderson, Project Manager, at (301) 594-0315. In future correspondence regarding this issue, please include a copy of this letter.

Sincerely yours,

/S/

Keith K. Chan, Ph.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDA 73-045

SEP 3 1996

A. L. Laboratories, Inc.
Attention: Deborah Miran
The John Hopkins Bayview Research Campus
333 Cassell Drive,
Suite 3500
Baltimore MD 21224

Dear Madam:

Reference is made to the Abbreviated New Drug Application amendments submitted on June 12 and 22, 1995, and July 31, 1996 for Albuterol Inhalation Aerosol, 90 mcg/Inhalation.

The Office of Generic Drugs has reviewed the bioequivalence data submitted and the following comments are provided for your consideration:

I. Comments pertaining to *In-Vivo* studies:

The following items are needed for completion of the evaluation of the *in-vivo* bioequivalence study. These items should be provided as paper copies (spread sheets) as well as on a floppy diskette (ASCII format):

1. Please provide complete raw data for all FEV_1 measurements, during screening and subject inclusion phases, and during the replicate design treatment phase for the 25 subjects used in the bioeqivalence study. This should include baseline FEV_1 measurements for each study day including subject screening and inclusion phase, as well as all FEV_1 measurements associated with each and every challenge dose. The number of breaths of methacholine associated with each and every challenge dose should also be reported.

   These data should include:

   a. ✓ Raw data on subject inclusion qualification criteria showing that there was a minimum increase over baseline in response to two actuations of Ventolin® Inhalation Aerosol and a minimum twofold ratio of response to two actuations relative to one actuation of Ventolin® Inhalation Aerosol. Include an example(s) of the method of calculation that was used for subject inclusion qualification criteria.

b. With regard to the data on the individual FEV_1 efforts for the bronchoprovocation study (data submitted on June 19, 1995, in two tables, located in volume B9.1, p #05-#25):

i. For **Table #1** (baseline FEV_1 data prior to morning and afternoon challenges for treatment phases only).

The data for subjects #113, 114, 115, 116, 119, 121, 122 (visits 1, 2 and 3) and 123 are not provided.

ii. For **Table #2** (raw FEV_1 data for treatment phases only).

The data for subjects #113, 114, 115, 116, 119, 121, 122 (visits 1, 2 and 3) and 123 are not provided.

2. Please provide the equation that was used to estimate the Post-albuterol PD_{20} (cumulative mg). In addition, please provide examples of your calculations for this value for a number of subjects. These examples should include subjects who had relatively high and relatively low post-albuterol PD_{20} values.

3. In the validation report section (Vol. A8.1, page #116), please provide equations and your calculations for subject #1, both morning and afternoon visits.

4. The raw data for the challenge studies should include the actual date of dosing of the treatment phase, gender and age, body weight, height, and predicted FEV_1 for age, gender and height, in addition to the data on baseline, saline control and FEV_1 at each challenge dose.

II. Comments pertaining to *In-Vitro* Studies:

1. Pivotal *in vitro* comparative cascade impactor data are unacceptable. The assay appears to be inadequately sensitive to quantitate drug on each stage of the Andersen[r] cascade impactor. Your use of actuations per study, in spite of the recommendation in the 1989 Division of Bioequivalence Guidance to use 15 actuations, emphasizes the need for improved assay sensitivity.

2. Material balance (USP 23 <601>), as requested in our July 18, 1996 letter was not provided. This calculation requires a knowledge of the actual shot weight, and measurement of drug concentration in the test and reference canisters. Drug concentration in

the canisters is determined by assay of total drug in canister, and weight of total contents. Your reported "% mass balance (1 Aug 96 amendment, Comment # 1 section, pp. 2-3) is not consistent with the USP material balance calculation.

3. Specific observations and concerns with the cascade impactor data will be discussed with you in the meeting scheduled for 9 Sep 96.

4. Particle size distribution by laser diffraction reports "best 3 results" without providing criteria for selection of best runs. The result reported for canister # 3 (test product), middle canister sector, appears to be a mean result, not that of an individual experiment. No indication of specific station (actuation) numbers were provided to identify beginning, middle and end canister sectors.

5. USP 23 <601> requests for single stage impactor apparatus 2 that unit dose from mean data of the Uniformity of Unit Spray Content study be used in the calculation of Respirable Percentage. You have stated that the mean unit dose for test and RLD products is 90.44 µg for the test product and 97.29 µg for the RLD. We note that you did not conduct Uniformity of Unit Spray Content (USP <905>) on both test and RLD products, thus Respirable Percentage data cannot be determined based on the USP method. The source of the mean unit dose data is not apparent.

6. Potency/unit spray content data will not be reviewed until the Division of Chemistry determines that the method is validated.

7. Specifications or revisions to specifications need to be considered for various tests, including respirable dose.

8. Particle size (distinct from particle size distribution) from the aerosol by microscopy, a standard test recommended by USP <601> to reveal large solid particles and agglomerates, has not been provided.

As described under 21 CFR 314.96 an action which will amend this application is required. The amendment will be required to address all of the comments presented in this letter. Should you have any questions, please call Mark Anderson, Project Manager, at (301) 594-0315.

In future correspondence regarding this issue, please include a copy of this letter.

Sincerely yours,

Keith K. Chan, Ph.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

V16.1

ANDA 73-045

A.L. Laboratories, Inc.
Attention: Deborah Miran
The Johns Hopkins Bayview Research Campus
333 Cassell Drive, Suite 3500
Baltimore, MD 21224

SEP 3 1996

Dear Madam:

This is in reference to your abbreviated new drug application dated December 28, 1988, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Albuterol Inhalation Aerosol, 90 mcg/Inhalation.

The following comments pertain to labeling issues only.

Due to the expiration of exclusivity for the "Prevention of exercise-induced bronchospasm in children ages 4-11 years" on July 20, 1996, we request that you revise your package insert labeling as described below.

1. CLINICAL PHARMACOLOGY

   Revise the last paragraph to read as follows:

   In other clinical studies involving both children and adults, two inhalations of albuterol aerosol taken...majority of patients. Two of these studies, one of which involved adults and the other children, also evaluated...in a majority...

2. INDICATIONS AND USAGE

   ...bronchospasm in patients 4 years of age...

3. DOSAGE AND ADMINISTRATION

   Exercise-Induced Bronchospasm Prevention

   ...and children 4 years and older...

Prepare and submit final printed labeling as an amendment. Please note that we reserve the right to request further changes in your labeling of the listed drug or upon further review of the application prior to approval.

To facilitate review of your next submission and in accordance with 21 CFR 314.94(a)(8)(iv), please provide side-by-side comparison of your proposed labeling with your last submission with the differences annotated and explained.

This letter addressed unique issues involving only labeling.

Sincerely yours,

/S/ 9/3/96

Jerry Phillips
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 73-045
Dup/Division File
HFD-600/Reading File C. Holquist 8/29/96 for 8/29/96
HFD-613/CHolquist/AVezza (no cc:)
njg/8/29/96/x:\firmsam\allabs\ltrs&rev\73045.LOL
Letter Out

ANDA 73-045

Alpharma, U.S.P.D
Attention: Vincent Andolina
The Johns Hopkins Bayview Research Campus
333 Cassell Drive, Suite 3500
Baltimore, MD 21224

MAY 20 1997

Dear Sir:

This is in reference to your abbreviated new drug application dated December 28, 1988, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Albuterol Inhalation Aerosol, 90 mcg/Inhalation.

Reference is also made to your amendments dated March 27, April 1, May 1, August 1, August 22, August 30, September 5, 9, 11, 20, and 30, October 8, and November 15, 1996 and January 6, and 22, and February 7, 1997.

The application is deficient and, therefore, Not Approvable under Section 505 of the Act for the following reason:

> Bioequivalency of the proposed product has not been demonstrated. Please submit your response to the letter dated May 12, 1997 issued by the Division of Bioequivalence concurrent with a response to this letter.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your response to this letter will be considered a MINOR amendment and should be so designated in your cover letter. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

Sincerely yours,

/S/ 5/19/97

for Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

ALPHARMA
U.S. Pharmaceuticals Division

August 6, 1997

Office of Generic Drugs
CDER, Food and Drug Administration
Attn: Mr. Douglas Sporn, Director
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

Re: **ANDA #73-045**
ALBUTEROL INHALATION AEROSOL, 90 mcg/INHALATION

TELEPHONE AMENDMENT TO A PENDING APPLICATION

Dear Mr. Sporn:

Pursuant to 21 CFR 314.96(a), Alpharma, U.S. Pharmaceuticals Division submits an amendment to the above referenced drug application. Reference is made to the teleconference of August 1, 1997 between Alan Rudman, Ph.D. (O.G.D., Division of Chemistry I, F.D.A.) and myself. Reference is also made to our drug application dated December 23, 1988. The Administration's comments have been restated and our responses follow.

Please change the drug product specifications as follows.

1. Identification test: Add an test for drug product release testing. The current retention time identification test is not sufficient.

2. Unit Spray Content test: Tighten the specifications from % for drug product release and stability testing.

Alpharma commits to revising its drug product release specifications to include an Identification test. Alpharma also commits to tightening the drug product release and stability specifications for Unit Spray Content from % of label claim* to % of label claim*.

Revised specifications and the test method will be submitted to the application post-approval.

Alpharma USPD Inc.
Research & Development Center
The Johns Hopkins Bayview Center
333 Cassell Drive, Suite 3500
Baltimore, MD 21224
Tel (410) 558-7250
Fax (410) 558-7258

Pursuant to 21 CFR 314.96(b), Alpharma certifies that the field copy is a true copy of this amendment to the application and has been sent to the Baltimore FDA District Office.

We trust that we have addressed the Agency's concerns.

Sincerely,
Alpharma

Ronald Bynum

Ronald Bynum
Manager, Regulatory Affairs

RB/rb
Enclosure

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ALPHARMA
U.S. Pharmaceuticals Division

Albuterol Inhalation Aerosol, 90 mcg/Inhalation
ANDA # 73-045

TELEPHONE AMENDMENT TO A PENDING APPLICATION

Pursuant to 21 CFR 314.96(b), Alpharma USPD certifies that the field copy is a true copy of the August 6, 1997 amendment to the application and has been sent to the Baltimore FDA District Office.

Ronald Bynum
Ronald Bynum
Manager, Regulatory Affairs

8/6/97
Date

f:\...\1264\submiss\080197td.ama

Alpharma USPD Inc.
Research & Development Center
The Johns Hopkins Bayview Center
333 Cassell Drive, Suite 3500
Baltimore, MD 21224
Tel (410) 558-7250
Fax (410) 558-7258

ALPHARMA
U.S. Pharmaceuticals Division

July 17, 1997

NDA CRG AMENDMENT

Office of Generic Drugs
CDER, Food and Drug Administration
Attn: Mr. Douglas Sporn, Director
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

Re: **ANDA #73-045**
ALBUTEROL INHALATION AEROSOL, 90 mcg/INHALATION

FAX TELEPHONE AMENDMENT TO A PENDING APPLICATION

Dear Mr. Sporn:

Pursuant to 21 CFR 314.96(a), Alpharma, U.S. Pharmaceuticals Division submits an amendment to the above referenced application. Reference is made to the teleconference of July 16, 1997 between Mr. Michael Smela (O.G.D., F.D.A.) and myself. Reference is also made to our drug application dated December 23, 1988. The Administration's comments have been restated and our responses follow.

Please revise the drug product specifications, both release and stability as follows:

The drug product must conform to the USP Content Uniformity specifications contained in <905>.

The Cascade Impactor specifications must be revised to:
MMAD:
GSD:
Respirable Fraction µm): Not Less Than
Respirable Dose (µm): Not Less Than µg/actuation.

Alpharma's current Content Uniformity specifications conform to the USP 23 specifications for Uniformity of Dosage Units <905>. However, Alpharma commits to rewording its drug product release and stability specifications to more closely match the wording in the USP specifications. Please note that the current drug product release specifications are located on pages 55-57 of our 9/5/96 amendment to the application. Our current drug product stability specifications are located on pages 5-6 of our 8/22/96 amendment to the application.

RECEIVED
JUL 18 1997
GENERIC DRUGS

Alpharma USPD Inc.
Research & Development Center
The Johns Hopkins Bayview Center
333 Cassell Drive, Suite 3500
Baltimore, MD 21224
Tel (410) 558-7250
Fax (410) 558-7258

Alpharma commits to revising its drug product release and stability specifications for Particle Size via Cascade Impaction to comply with the requested specifications of MMAD (Mass Median Aerodynamic Diameter) = 1.5 - 3.5; GSD (Geometric Standard Deviation) = 1.0 - 2.0; Respirable Fraction (≤ 4.7 µm) = Not Less Than 0.3; and Respirable Dose (≤ 4.7 µm) = Not Less Than 27 µg/actuation.

Revised specifications will be submitted to the application post-approval.

Pursuant to 21 CFR 314.96(b), Alpharma certifies that the field copy is a true copy of this amendment to the application and has been sent to the Baltimore FDA District Office.

We trust that we have addressed the Agency's concerns.

Sincerely,
Alpharma

Ronald Bynum

Ronald Bynum
Manager, Regulatory Affairs

RB/rb
Enclosure
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ALPHARMA
U.S. Pharmaceuticals Division

NDA ORIG AMENDMENT
AM

May 27, 1997

Office of Generic Drugs
CDER, Food and Drug Administration
Attn: Mr. Douglas Sporn, Director
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

Re: **ANDA #73-045**
ALBUTEROL INHALATION AEROSOL, 90 mcg/INHALATION

MINOR AMENDMENT TO A PENDING APPLICATION

Dear Mr. Sporn:

Pursuant to 21 CFR 314.96(a), Alpharma, U.S. Pharmaceuticals Division submits an amendment to the above referenced application. Reference is made to the Administration's May 20, 1997 correspondence pertaining to bioequivalency issues (attached). Reference is also made to our bioequivalence amendment dated May 23, 1997 and to our drug application dated December 23, 1988. The Administration's comments have been restated and our response follows.

The application is deficient and, therefore, Not Approvable under Section 505 of the Act for the following reason:

Bioequivalency of the proposed product has not been demonstrated. Please submit your response to the letter dated May 12, 1997 issued by the Division of Bioequivalence concurrent with a response to this letter.

The response to the Division of Bioequivalence's letter dated May 12, 1997 was submitted on May 23, 1997. A copy of our response is attached.

We trust that we have addressed the Administration's concerns.

Sincerely,

RECEIVED
MAY 28 1997
CDER/ONDC DRUGS

Ronald Bynum
Ronald Bynum
Manager, Regulatory Affairs

RB/rb
Enclosure

Alpharma USPD Inc.
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6.3.97

ALPHARMA
U.S. Pharmaceuticals Division

NEW CORRESP

BIOAVAILABILITY

May 23, 1997

Office of Generic Drugs
CDER, Food and Drug Administration
Attn: Mr. Douglas Sporn, Director
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

Re: **ANDA #73-045**
ALBUTEROL INHALATION AEROSOL, 90 mcg/INHALATION

BIOEQUIVALENCE AMENDMENT TO A PENDING APPLICATION

Dear Mr. Sporn:

Pursuant to 21 CFR 314.96(a), Alpharma, U.S. Pharmaceuticals Division submits an amendment to the above referenced application. Reference is made to the teleconference of February 28, 1997 between Dr. Wallace Adams and Ms. Lizzie Sanchez (D.O.B., O.G.D., F.D.A.) and Dr. Robert Shumaker and Mr. Ron Bynum of Alpharma. Reference is also made to the March 5, 1997 telefax and the May 12, 1997 letter (attached) summarizing the deficiencies discussed in the February 28, 1997 teleconference. Reference is also made to our drug application dated December 23, 1988. The Administration's comments have been restated and our responses follow.

1. **Because drug delivery may change progressively through canister life, the Division of Bioequivalence believes that, as a bioequivalence criterion, a test product should meet USP <905> Content Uniformity requirements at beginning, middle and end of canister through-life. Therefore, the firm is requested to provide the following:**

   a. **Content uniformity data on 30 canisters of test lot # 8457 at beginning, middle and end.**

   Content uniformity (potency) data on 30 canisters from the beginning, middle, and end are provided on pages. The data conform to the USP <905> content uniformity specifications in that 28 of 30 of the beginning results are within % of claim and 2 of 30 values are outside of % but within % of claim; all 30 middle results are within % of claim; and 27 of 30 of the end results are within % of claim and 3 of 30 values are outside of % but within % of claim.

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MAY 27 1997

When we include the content uniformity data for this batch that was previously submitted as page 430 of our January 6, 1997 submission, 38 of 40 of the beginning results are within [% of claim and 2 of 40 values are outside of % but within [% of claim; 37 of 40 middle results are within % of claim and 3 of 40 values are outside of % but within [% of claim; and 37 of 40 of the end results are within [% of claim and 3 of the 40 values are outside of % but within [% of claim.

The test method for the content uniformity testing is enclosed as pages 011-014. The [parameters are located within test method (Unit Spray Content & Total Number of Shots per Can) (pages 015-019).

b. **Content uniformity data on 10 canisters of test lots # 8671 and 8834 at beginning, middle and end. For each batch, if 10 canisters fail to meet the USP specification at each of beginning, middle and end, an additional 20 canisters should be tested as stated in USP <905>. Note that, consistent with the 27 June 1989 Division of Bioequivalence *Guidance for the In Vitro Portion of Bioequivalence Requirements for Metaproterenol Sulfate and Albuterol Inhalation Aerosols (Metered Dose Inhalers)*, the specifications will be evaluated separately at beginning, middle and end of canister through life.**

Content uniformity (potency) data on 10 canisters from the beginning, middle, and end of batch #8671 are provided on pages 007-008. The data conform to the USP <905> content uniformity specifications in that 10 of 10 of the beginning results are within [% of claim; 9 of 10 middle results are within [% of claim and 1 of 10 values is outside of % but within [% of claim; and 10 of 10 of the end results are within % of claim.

Content uniformity (potency) data on 10 canisters from the beginning, middle, and end of batch #8834 are provided on pages 009-010. The data conform to the USP <905> content uniformity specifications in that 10 of 10 of the beginning results are within [% of claim; all 10 middle results are within [% of claim; and 10 of 10 of the end results are

within [redacted]% of claim.

c. **Data may be provided in the same format as that on pages 430 and 431 of the 6 January 1997 submission.**

The data are provided in a similar format as previously provided on pages 430 and 431 of our January 6, 1997 submission. The summary table at the bottom of the data summary page has been revised to separately summarize the results for the beginning, middle, and end of the canisters. The data is also included on an Excel formatted diskette for ease of review (page 020). A listing of the file directory is included.

2. **Additional information is also requested by the Division of Bioequivalence:**

a. **The specific model of Andersen 8 stage cascade impactor used by the firm for the data submitted on 6 January 1997.**

The cascade impactor used in the in vitro study submitted on January 6, 1997 was model number Andersen

b. **The expiration dates for test product batches # 8671 and 8834.**

Albuterol Inhalation Aerosol, batch #8671 has an expiration date of February, 1998.

Albuterol Inhalation Aerosol, batch #8834 has an expiration date of April, 1998.

c. **Testing dates for the twin impinger data submitted on 12 June 1995 and 27 July 1996.**

Alpharma did not make any submissions to this application with the date of 27 July 1996. Twin impinger data with a fax date of "27-JUL. '96(SAT)" were submitted as pages 162 and 163 in our August 1, 1996 amendment to the application.

Twin impinger testing for Albuterol Inhalation Aerosol, lot #6403 was conducted on December 12, 1993 in conjunction with the 3 month stability test station for this batch. For Ventolin® Inhalation Aerosol, lot

#Z31383LS, twin impinger testing was performed on February 17, 1994. Data from both batches were submitted as page 615 of our June 12, 1995 submission.

In response to the July 18, 1996 bioequivalence deficiency letter, the data were recalculated to provide the amount of drug in both stages, the average shot dose (unit spray content), and the respirable fraction. These data were provided as pages 162 and 163 of our August 1, 1996 submission. The shot dose data (unit spray content) were obtained from the potency data submitted as pages 626 and 627 of the June 12, 1995 submission.

In response to the September 3, 1996 bioequivalence deficiency letter, the data were recalculated to utilize unit dose values (unit spray content) from mean data in calculation of the respirable percentage. These data were provided as pages 108 and 109 of our September 9, 1996 submission. The unit dose data (unit spray content) were obtained from the retest potency data that were submitted as pages 110 and 111 of our September 9, 1996 submission.

d. **Conduct of the Microscopy Test (USP <601>) on canisters from test product batches # 8457, 8671, and 8834, and Ventolin MDI batch # 6ZP0756. The Division requests these comparative baseline data, noting that the test serves a number of purposes: determination of the number of particles larger than 10 microns; identification of unusual agglomeration; characterization of crystal morphology; and identification of foreign particulates not related to the drug substance.**

We have conducted the microscopy particle size test on test batches #8457, 8671, and 8834, and Ventolin® MDI batch #6ZP0756. The data summary is located on pages 302-303. No particles greater than microns in length (the longest dimension) were observed in any of the 25 fields of view for any of the three canisters for each of the four lots tested. No agglomerations nor foreign particulates were observed. The crystal morphology in all lots was classified as irregular crystalline material of approximately [ ] microns. The measuring device was calibrated against a μm graticule to assure that the system was capable of detecting and measuring particles greater than μm

(page 304). Photographs of representative fields of view at both 100 X and 40 X magnification are provided for each of the four batches that were analyzed (pages 321-332). The microscopy particle size test method is enclosed as pages 333-334.

We trust that we have addressed the Agency's concerns.

Sincerely,
Alpharma

Ronald Bynum
Manager, Regulatory Affairs

RB/rb
Enclosure
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13-095

ALPHARMA™ NEW CORRESP

U.S. Pharmaceuticals Division

NL NAF JB 2-27-97

February 7, 1997

Office of Generic Drugs
CDER, Food and Drug Administration
Attn: Mr. Douglas Sporn, Director
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

Re: **Contact Persons for Abbreviated New Drug Applications and Abbreviated Antibiotic Drug Applications**

Dear Mr. Sporn,

Reference is made to the February 3, 1997 teleconference between Mr. Joe Buccine (OGD, FDA) and Mr. Ronald Bynum (Alpharma) concerning contact persons for abbreviated applications. A listing of Alpharma U.S.P.D's abbreviated applications and the respective contact persons is attached. Alpharma requests that FDA's queries pertaining to Alpharma's applications be addressed to either Mr. Vincent Andolina, Senior Manager, Regulatory Affairs at (410) 558-7250, extension 209 or Mr. Ronald Bynum, Senior Manager, Regulatory Affairs at (410) 558-7250, extension 208, as indicated on the attached listing. Both individuals have offices located at the following address:

Alpharma, U.S.P.D.
Johns Hopkins Bayview Campus
333 Cassell Drive, Suite 3500
Baltimore, MD 21224

Telefax: (410) 558-7258.
Alternate telefax: (410) 558-7262.

Sincerely,

Stanley A. Kaplan, Ph.D.
Senior Vice President
Research and Development

enclosure
SK:rb

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Research & Development Center
The Johns Hopkins Bayview Campus. 333 Cassell Drive. Suite 3500. Baltimore. MD 21224
Tel: (410) 558-7250 Fax. (410) 558-7262

ALPHARMA
U.S. Pharmaceuticals Division

January 6, 1997

[redacted] CORRESP BIOAVAILABILITY

NC 16

Office of Generic Drugs
CDER, Food and Drug Administration
Attn: Mr. Douglas Sporn, Director
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

Re: **ANDA #73-045**
ALBUTEROL INHALATION AEROSOL, 90 mcg/INHALATION

TELEPHONE BIOEQUIVALENCE AMENDMENT TO A PENDING APPLICATION

Dear Mr. Sporn:

Pursuant to 21 CFR 314.96(a), Alpharma, U.S. Pharmaceuticals Division submits an amendment to the above referenced application. Reference is made to the issues contained in the November 21, 1996 telefax (attached) and to the November 21, 1996 teleconference between representatives of FDA's O.G.D. (Dr. Wallace Adams, Dr. Rabindra Patnaik, and Mark Anderson) and Alpharma (Deborah Miran, Ronald Bynum, and Dr. Richard Dalby, University of Maryland, School of Pharmacy) and to our drug application dated 12/23/88. Reference is also made to the Agency's correspondence of 7/21/91, 6/3/94, 8/11/94, 5/26/95, 1/29/96, 4/8/96, 7/18/96, 8/22/96, 8/23/96, 9/3/96, 9/25/96, and 10/28/96 and to Alpharma's correspondence of 2/4/94, 2/14/94, 12/2/94, 1/27/95, 6/12/95, 6/22/95, 8/1/95, 2/23/96, 5/1/96, 8/1/96, 8/22/96, 9/5/96, 9/9/96, 9/11/96, 9/20/96, 9/30/96, 10/8/96, and 11/15/96.

The Agency's comments from the 11/21/96 teleconference have been restated and our responses follow.

1. **Prior to conducting its cascade impactor studies, the firm should conduct analytical validation of its [redacted] assay method, based on standard validation procedures, as described in: VP Shah et al., "Analytical Methods Validation: Bioavailability, Bioequivalence and Pharmacokinetic Studies." Pharm Res. 9:588-92 (1992). The firm is specifically referred to sections entitled:**

   a. **"Principles of Methods Validation-Methods Establishment,"**

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b. "Specific Recommendations for Methods Validation", and
c. "Acceptance Criteria for the Run".

The firm is advised that the data provided in the 15 Nov 96 amendment ("System Suitability and Standard Recovery Data" section), allows estimation of precision at mcg/mL and mcg/mL, but doesn't allow estimation of accuracy. A standard curve over the range of concentrations necessary to assay solutions from the cascade impactor study has not been provided.

Concentrations of all calibrators, quality control (QC) samples, and replicate runs should be provided. Any relevant SOP's should be submitted along with the validation report. These validation data should be conducted in the same laboratory that will conduct the comparative side-by-side cascade impactor studies.

Analytical methods validation for the procedure utilized in testing samples from the in vitro cascade impactor study and the unit spray content (potency) study was performed at CCL incorporating the concepts referenced in the journal article pertaining to methods validation. The methods validation report is enclosed as pages 002-021. Raw data from the methods validation is enclosed as pages 022-120.

2. The firm is requested to provide comparative cascade impactor studies of test and reference products for at least one lot each of test and RLD products that are within-expiry, based on the Division of Bioequivalence *In Vitro* Guidance. Studies should be conducted on three canisters of test and three canisters of RLD at beginning, middle and end canister sectors. Although 15 actuations per study is preferred, the firm may continue to use data based on 25 actuations. These studies should be conducted as side-by-side experiments, i.e., within the same time period and within the same laboratory. The firm may also wish to conduct the cascade impactor study on three canisters of an additional lot of test product (beginning sector only).

A comparative cascade impactor study between test drug product within expiry (Albuterol Inhalation Aerosol, lot #8457, expiration 12/97) and reference drug product within expiry (Ventolin® Inhalation Aerosol, lot #6ZP0756, expiration 04/99) was conducted. The data from the cascade

impactor study are contained within section #3.

It should be noted that the comparative cascade impactor study was performed using the recommended 15 actuations per study. The test method used for the in vitro cascade impactor study is located on pages 121-124. A listing of the changes between the current method and the previous cascade impaction method is contained on pages 125-126.

The cutoff diameters for the cascade impactor device used for the current cascade impactor study were obtained from calibration of the device (pages 127-128). The cascade impactor was calibrated to comply with the USP 23 General Chapters section for Physical Tests and Determinations, sub-section Aerosols <601> (USP 23 page 1763). Therefore, the theoretical cutoff diameters from Andersen were not used. The difference in cutoff diameters affect MMAD and GSD, but do not affect quantity of drug collected on a particular stage.

CALIBRATION — SEE PP. 127-8

The cascade impactor study was also conducted on the beginning sector of two additional lots of the test drug product within expiry (Albuterol Inhalation Aerosol, lot #8671 and lot #8834). The cascade impactor study data for these two additional lots are located within section #3. The batch records for each of these additional lots are located on pages 129-160 and 161-194, respectively.

3. Cascade impactor data should be provided as a hard copy as well as in Excel-formatted spreadsheets, and should include:

a. all raw data sheets, showing tabulations of concentrations of solutions at all stages, actuator, atomizing chamber, and filter (and valvestem, if desired).

Raw data from the cascade impactor studies, in the form of spreadsheets, are provided as pages 195-275.

Albuterol Inhalation Aerosol, lot #8457 (pages 196-223).
Ventolin® Inhalation Aerosol, lot #6ZP0756 (pages 224-251).
Albuterol Inhalation Aerosol, lot #8671 (pages 252-261).
Albuterol Inhalation Aerosol, lot #8834 (pages 262-275).

The concentrations of standard solutions are located on pages 1 and 2 of each study spreadsheet; the concentrations of sample solutions are located on page 2 of each study spreadsheet.

Raw data from the chemist's notebook are contained on pages 276-310. The dilution volumes for the standards and samples are listed on pages 311-314.

b. QC sample data should be provided for within-run validation.

The drug product is composed of albuterol base, oleic acid, propellant 11 and propellant 12. During the collection of the samples in the cascade impactor, the two propellants evaporate. The oleic acid is not detectable in the assay system used for analysis. Since there was no component within the drug product that interfered with the assay of albuterol and since the assay diluent is mobile phase, preparation of samples in sample matrix was not necessary. The QC "samples" utilized for the cascade impactor study were composed of known concentrations of albuterol base in the assay diluent. A summary of the QC sample data is enclosed as pages 316-317. The QC "sample" data are located on pages 318-340. A summary of the calibrators is enclosed as page 341 and the raw data for calibrators is enclosed as pages 342-347.

c. separate tables should provide the amounts of drug on all stages, actuator, atomizing chamber, and filter (and valvestem, if desired).

Separate data summary tables are located on pages 348-368.

Albuterol Inhalation Aerosol, lot #8457 (pages 348-352).
Ventolin® Inhalation Aerosol, lot #6ZP0756 (pages 353-357).
Albuterol Inhalation Aerosol, lot #8671 (pages 358-362).
Albuterol Inhalation Aerosol, lot #8834 (pages 363-368).

A copy of the cascade impactor study data summaries (and potency summaries) have been included on an Excel formatted disk for review (page 369).

An evaluation of the cascade impactor study data is enclosed as pages 371-372 for quantity of drug collected and pages 373-374 for percent material

balance.

d. representative chromatograms showing concentrations of drug at stages with high and low drug deposition.

Representative chromatograms are enclosed on pages 375-394.

Albuterol Inhalation Aerosol, lot #8457 (pages 375-379).
High drug deposition (pages 375-377).
Low drug deposition (pages 378-379).

Ventolin® Inhalation Aerosol, lot #6ZP0756 (pages 380-384).
High drug deposition (pages 380-382).
Low drug deposition (pages 383-384).

Albuterol Inhalation Aerosol, lot #8671 (pages 385-390).
High drug deposition (pages 385-387).
Low drug deposition (pages 388-390).

Albuterol Inhalation Aerosol, lot #8834 (pages 391-394).
High drug deposition (pages 391-392).
Low drug deposition (pages 393-394).

e. assay of drug in test and RLD canisters, in order to compute Percentage Material Balance, as calculated by USP <601>.

The assay data for the total contents of the canister are located on pages 395-422.

The summary of concentration of drug in the formulation is enclosed as pages 423-426.

Albuterol Inhalation Aerosol, lot #8457 (page 423).
Ventolin® Inhalation Aerosol, lot #6ZP0756 (page 424).
Albuterol Inhalation Aerosol, lot #8671 (page 425).
Albuterol Inhalation Aerosol, lot #8834 (page 426).

4. Comparative potency data is requested for ten canisters of test product and ten canisters of RLD, as described in the Division of Bioequivalence *In Vitro* Guidance. These data will be assessed, in part, according to the USP Uniformity of Unit Spray Content criteria, as stated in USP <905>.

Comparative potency data from ten canisters of the test drug product (Albuterol Inhalation Aerosol, lot #8457; expiration 12/97) and the reference drug product (Ventolin® Inhalation Aerosol, lot #6ZP0756; expiration 04/99) are provided on page 430 and 431, respectively. The test method for the in vitro potency study is located on pages 470-472. A listing of the changes between the current method and the previous unit spray content (potency) method is contained on page 473.

5. **The firm is requested to confirm its computation of 'Respirable Dose', as reported on page 101 of the "Retest Cascade Impactor" section of the 9 Sep and 11 Sep 96 amendments. These values do not agree with computations of respirable dose reported in other amendments by the firm. In addition, spot check shows that a minor % error appears to occur on page 101 for 'D' (Mass of drug expected to have been delivered) for Canister #1 (middle).**

The "Respirable Dose" values reported on page 101 of the Retest Cascade Impactor section of the 9 Sep amendment have been re-evaluated. The respirable dose μm ranged from The value was a typographical error, with the correct value being (a corrected summary for Albuterol Inhalation Aerosol, lot #6403 is provided as page 501). The range of values from the 9 Sep 96 amendment was similar to the range of respirable dose values of submitted in the 1 Aug 96 amendment. The range of respirable dose values of submitted in the 8 Oct 96 amendment also fell within this range. A same trend of similar ranges was found for the respirable dose μm when comparing values in the 9 Sep 96, 1 Aug 96 and 8 Oct 96 amendments.

The % error in the "D" value for the middle of canister #1 is due to a transcription error. The correct value is mg as calculated on page 104 of the 9 Sep 96 amendment (a corrected summary is provided as page 501 and an indication of the corrections is provided as page 500).

A corrected summary for Ventolin® Inhalation Aerosol, lot #Z31383LS is provided as page 503 and an indication of the corrections is provided as page 502.

6. **Inconsistencies in cascade impactor stage cutoff data (microns) appear in the 9 Sep 96 and 8 Oct 96 amendments. Five different sets of cutoff diameters are listed by the firm (refer to page 100 of the 9 Sep 96 amendment, and to pages 3, 7, 8 and 11 of the 8 Oct 96 amendment). Only the values in the 9 Sep 96 amendment agree with the values stated in the "Operating Manual for Andersen 1 ACFM Non-**

Viable Ambient Particle Sizing Samplers". The text [D. Cooper, Aerosol Measurement Principles. Techniques and Applications, eds. K. Willeke and P. Baron, Chap 9, pp. 146-176, Van Nostrand Reinhold, NY (1993)] is referenced with no explanation.

Inconsistencies in cascade impactor cutoff data are due to use of multiple impactors; use of the theoretical cutoff diameters as supplied by the device manufacturer; use of calibrated cutoff diameters following calibration of the device; and erroneous values. The cutoff values listed on pages 7 and 8 of the 8 Oct 96 amendment are carryovers from a different cascade impactor study. The cutoff diameters were previously entered into the spreadsheets and these values were not changed when the data tables for the referenced study were prepared. The different cutoff diameters do not affect quantity of drug collected on a articular stage. The different cutoff diameters do however, affect MMAD and GSD.

As noted in the response to observation #2 above, calibrated cutoff diameters were used for this current comparative cascade impactor study.

The reference to author Cooper's book chapter also is a carryover of the spreadsheet. The reference pertains to graphic presentation of particle size distributions. We have included a copy of the relevant pages of the referenced book chapter, not the entire chapter (pages 158-161 of the book) (pages 504-507 of this amendment).

We trust that we have addressed the Agency's concerns.

Sincerely,
Alpharma, U.S. Pharmaceuticals Division

Ronald Bynum

Ronald Bynum
Manager, Regulatory Affairs

RB/rb

Enclosure
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Dick E Bio (2nd)

ALPHARMA
U.S. Pharmaceuticals Division

ORIG NDA 73-045

November 15, 1996

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Office of Generic Drugs
CDER, Food and Drug Administration
Attn: Mr. Douglas Sporn, Director
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

Re: **ANDA #73-045**
ALBUTEROL INHALATION AEROSOL, 90 mcg/INHALATION

TELEPHONE BIOEQUIVALENCE AMENDMENT TO A PENDING APPLICATION

Dear Mr. Sporn:

Pursuant to 21 CFR 314.96(a), Alpharma, U.S. Pharmaceuticals Division submits an amendment to the above referenced application. Reference is made to the October 28, 1996 teleconference between representatives of FDA's O.G.D. (Gordon Johnston, Wallace Adams, and Mark Anderson) and Alpharma (Ronald Bynum) and to our drug application dated 12/23/88. Reference is also made to the Agency's correspondence of 7/21/91, 6/3/94, 8/11/94, 5/26/95, 1/29/96, 4/8/96, 7/18/96, 8/22/96, 8/23/96, 9/3/96, and 9/25/96, and to Alpharma's correspondence of 2/4/94, 2/14/94, 12/2/94, 1/27/95, 6/12/95, 6/22/95, 8/1/95, 2/23/96, 5/1/96, 8/1/96, 8/22/96, 9/5/96, 9/9/96, 9/11/96, 9/20/96, 9/30/96, and 10/8/96.

The Agency's comments from the 10/28/96 teleconference have been paraphrased and our responses follow.

1. **Please supply assay validation data over the range of drug measured. If appropriate, supply both inter-day and intra-day validation. Indicate when the validation was conducted, ie., for which set of data (pre-expiry of the bio-batch, post-expiry of the bio-batch, or the new batch). The Limit of Quantitation value submitted on 10/8/96 was less sensitive than the Limit of Detection value previously submitted. How was this value determined?**

   The test method used by CCL is the same for all tests (Unit Spray Content, Content Uniformity Deposition of Emitted Dose by Twin Impinger Type II, Cascade Impaction, and Content of Albuterol per can) with a few slight differences. The

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differences are in injection volume (either μL) and/or concentration of the standard and sample solutions (either μg/mL).

Validation data for Content Uniformity Through the Actuator were previously submitted as pages 499-530 of the 2/4/94 amendment. This validation included data for Linearity, Accuracy, Precision, and Ruggedness (pages 2-37 of this amendment). A copy of the raw data for the Content Uniformity validation is enclosed as pages 86-106.

Validation data for the Finished Product Assay (Content of Albuterol per Can) were previously submitted as pages 003-044 of the 12/2/94 amendment. This validation included data for Linearity, Accuracy, Precision, Ruggedness, Specificity, and Limit of Detection (pages 38-84 of this amendment). A copy of the raw data for the Finished Product Assay (Content of Albuterol per Can) is enclosed as pages 107-123.

Validation data for Cascade Impaction has previously been submitted as pages 3-46 of the 9/11/96 amendment and pages 168-211 of the 12/2/94 amendment. The validation included data for Linearity, Accuracy, Precision, and Ruggedness (pages 124-168 of this amendment).

Since the test method for Content Uniformity, Finished Product Assay (Content of Albuterol per can), and Cascade Impaction, are basically the same, assay validation has been conducted three times. A table summarizing the data is enclosed as page 169.

A review of the cascade impaction data previously submitted to the application reveals that data in the range of μg/mL have been submitted. The validation of Content Uniformity has linearity data in the range of μg/mL to μg/mL. The validation of Finished Product Assay (Content of Albuterol per Can) has linearity data in the range of μg/mL to μg/mL.

When we re-evaluated the linearity data from the Content Uniformity validation and inserted a zero response for a zero concentration, the Regression Coefficient, R, changed from R = 0.998282504 to R = 0.998272371 (page 170). This difference is not significant, thus demonstrating linearity between the range of μg/mL. This range covers the cascade impaction data collection range of μg/mL.

Therefore, we have validation data in the concentration range of drug collected within the cascade impaction device.

As stated previously, we have performed validation three times for the test method. To assure that the method is performing satisfactorily on the day that tests are performed, we conduct system suitability testing (limit = RSD Not More Than %) and we conduct a standard recovery test (limit = 98.0 % to 102.0% difference between two separate standards). This testing assures satisfactory performance of the test method each time that it is performed. The system suitability and standard recovery data from the cascade impaction testing pre-expiry of the bio-batch, post-expiry of the bio-batch, and for the new batch (lot #8457) are enclosed as pages 171-175 and 176-182. It should be noted that the dates on the summary sheets are the dates that the data were tabulated, while the dates on the chromatograms are the dates that the injections were made. The re-testing for lot #6403 and the testing for lot #8457 were conducted at the same time, therefore the data for these two tests are combined.

The raw data for the Limit of Quantitation test are enclosed as pages 183-191. The acceptance criterion for Limit of Quantitation was defined as a Relative Standard Deviation of less than ten percent (RSD < 10%).

2. Please supply stability data for the test drug product outside expiry.

The stability program for the bio-study lot, lot #6403, ended after the 24 months stability test station. However, in response to questions from FDA's Bioequivalence personnel, we performed additional testing on this batch. Data for Identification, Shot Weight, Unit Spray Content, Cascade Impaction, and Spray Pattern have been included with the stability summaries (pages 192-196). The Unit Spray Content data measure drug delivered through the actuator and thus measures drug available to the patient. Cascade Impaction measures drug particle size and thus determines drug available to patients in the respirable range. These tests are the most important stability tests since they measure drug provided to the patient. Since the other stability tests are less important in determining drug available for patients, we have not performed the complete battery of stability tests post-batch expiration.

3. For the new drug product lot that was submitted in the chart on 10/8/96, please supply the data on a disc in ASCII format, to be read by Excel.

The cascade impaction data for drug product lot #8457 are provided on a diskette in ASCII format for Excel. The data from the charts on pages 02 to 04 of the October 8, 1996 amendment have been included on the diskette. A hard copy of the data contained on the diskette is enclosed as pages 197-199.

4. Please confirm the source of the data on pages 07-08 of the 10/8/96 submission. The testing source could not be determined since the company name on the pages containing the chromatograms (pages 05-06) could not be read. If the testing were done by an additional laboratory, then please supply inter-laboratory validation data to support this testing.

The data on pages 02 to 06 of the October 8, 1996 submission were generated by CCL. New copies of the chromatograms, with the company name unobscured are enclosed as pages 200-201. The data summary sheets with the[ ]footers were prepared by Alpharma, from the CCL data contained on pages 02 to 04 of the 10/8/96 amendment. Alpharma used a spread sheet from[ ]to display the CCL data from the "start" of can 1.

We trust that we have addressed the Agency's concerns.

Sincerely,
Alpharma, U.S. Pharmaceuticals Division

Deborah Miran
Sr. Director, Regulatory Affairs

DM/rb

Enclosure
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ALPHARMA™
U.S. Pharmaceuticals Division

BIOAVAILABILITY

NEW CORRESP

October 8, 1996

Office of Generic Drugs
CDER, Food and Drug Administration
Attn: Mr. Douglas Sporn, Director
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

RECEIVED
OCT 0 9 1996
GENERIC DRUGS

Re: **ANDA #73-045**
ALBUTEROL INHALATION AEROSOL, 90 mcg/INHALATION

AMENDMENT TO A PENDING APPLICATION

Dear Mr. Sporn:

Pursuant to 21 CFR 314.96(a), Alpharma, U.S. Pharmaceuticals Division submits an amendment to the above referenced application dated December 23, 1988. Reference is made to additional FDA requests made during the September 9, 1996 meeting pertaining to the in vitro bioequivalence study. Reference is also made to the FDA correspondence of 7/18/96 and 9/3/96 and to our correspondence dated 6/12/95, 8/1/96, 9/9/96, and 9/11/96.

A detailed list of attachments follows on the page entitled "Index of Supporting Documents".

We trust that we have addressed the Agency's concerns.

Sincerely,

Deborah Miran
Sr. Director, Regulatory Affairs

DM
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f:\...\1264\submiss\invitro.tel

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